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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/733,756	12/08/2000	David Mack	A-69439/DJB/JJD	2798

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EXAMINER	
GOLDBERG, JEANINE ANNE	

ART UNIT	PAPER NUMBER
1634	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

called 12/23
left message
12/31 w/ time 1/7/03

Office Action Summary	Application No. 09/733,756	Applicant(s) MACK ET AL.	
	Examiner Jeanine A Goldberg	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-30 and 32-47* is/are pending in the application.

4a) Of the above claim(s) *1-6 and 8-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 December 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Amendments to the Claims

1. This action is in response to the election made on May 31, 2002. Claims 7, 31 were cancelled and Claims 32-47 were added. Claims 32-47 have been examined on the merits. Claims 1-6, 8-30 have been withdrawn from consideration as drawn to non-elected claims.

Election/Restrictions

2. Applicant's election with traverse of Group V, Newly added Claims 32-47 in Paper No. 11 is acknowledged.

The response argues that the inventions of the present application can be readily searched without undue burden. This argument has been reviewed, but deemed not persuasive. The original restriction requirement provided that numerous groups were classified in different classes. For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation of separate classification, or separate status in the art, or a different field of search as defined in MPEP § 808.02. Moreover, the restriction provided the different fields of searches required. A search of the subject matter of invention V is not co-extensive with a search of inventions I-IV, VI-XI.

The requirement is still deemed proper and is therefore made FINAL.

Priority

3. This application claims priority to 09/525,993, filed March 15, 2000; 09/493,444, filed January 28, 2000; 09/453,850, filed December 2, 1999.

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

It is noted that the instant gene, SEQ ID NO: 1, CHA4 does not appear to be supported by the earlier filing dates. In the event that the sequence and the association with breast cancer or colorectal cancer may be found in one of the earlier applications, the applicant is invited to point out such support.

Drawings

4. The drawings are objected by the examiner.

Figures 1 and 2 contain sequences. The sequences are neither identified by SEQ ID NO: on the figure or in the figure legend. The figure legend for Figure 1 states that the start and the stop codons are underlined. Figure 1 only appears to contain a single underline of TAG. Therefore, it does not appear that the start codon is underlined.

Figure 3A-D have holes in the vertical axis. Increasing the top margin of the page would eliminate the holes in the axis.

Specification

5. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

For example, page 11 contains a website.

6. The title of the invention is not descriptive of the elected invention. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 32-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are broadly drawn to a method for diagnosing breast cancer or colorectal cancer by determining the expression level of a gene which is at least 75% identical to SEQ ID NO: 1.

The specification teaches that SEQ ID NO: 1 corresponds to the gene CHA4. CHA4 nucleic acid and amino acid sequences are shown in Figure 1 and 2, respectively. Figures 3A illustrates the relative amount of expression of CHA4 in various samples of breast cancer tissue; Figure 3B illustrates colorectal cancer tissue; and Figures 3C-3D illustrate several normal tissue types. With respect to Figure 3A directed to breast cancer tissue, the expression level in the tissues appears to range from 100-750 (no units provided). Turning to Figure 3C, normal breast tissue appears to range from 80-400 (no units provided). As seen in Figure 3A, 54 of the samples had expression within the "normal" range of expression. 54 of the 66 (83%) breast cancer tissues had expression levels less than 400. Therefore, there does not appear to be

differential expression between the breast cancer tissues of Figure 3A and the 7 breast normal tissues of Figure 3C.

With respect to Figure 3B directed to colorectal cancer tissue, the expression level in the numerous tissues appears to range from 100-740 (no units provided). Turning to Figure 3C, normal colon appears to range from 100-200. 11 of the 78 (14%) colorectal tissues had expression levels less than 200. Therefore, the ranges of normal and cancerous expression levels of CHA4 overlap.

The art teaches what is called CHA4 in the specification has also been referred to as Ephrin-A3, EphA3, hek-L, Lerk-3, ehk1-L, and Ehk1. Beckmann et al. (US Pat. 5,516,658, May 1996) teaches Hek ligand (hek-L) polypeptides and nucleic acids encoding the polypeptides. The Hek-L polypeptides, SEQ ID NO: 2 of Beckmann and SEQ ID NO: 2 of the instant application are 100% identical over all 238 amino acids. The nucleic acid of Beckmann, namely SEQ ID NO: 1 and the instant SEQ ID NO: 1 share 52.7% identity over the full length with a best local similarity of 99.8% (see attached alignment). Beckmann teaches a human T-cell leukemia cell line expresses the Hek-L nucleic acid. Beckmann does not specifically teach using the Hek-L for diagnostic of cancers.

Neither the specification nor the art teach the skilled artisan how to use the invention as broadly as claimed. The specification and claims of the instant application assert that detection of the expression of a gene comprising at least 75% identity with SEQ ID NO: 1 allows for diagnosis of colorectal cancer. The evidence for this assertion provided in the specification, in Figure 3A-3D, Example 3, page 68, does not appear to

support the assertion. As provided in the analysis above, the ranges for "normal" and "cancerous" tissue expression of CHA4 overlap in both breast and colon cancers analyzed. There is no indication in the specification of a threshold which would be indicative of colon or breast cancer tissue. Therefore, distinguishing a cancerous tissue from a normal tissue based solely on different sample expression would be unpredictable. While one could conduct additional experimentation to determine whether, e.g., expression of SEQ ID NO: 1 at certain levels might be associated with, e.g., certain types of colorectal or breast cancers, the outcome of such research cannot be predicted, and such further research and experimentation are both unpredictable and undue.

Furthermore, the teachings of the prior art do not provide evidence of how to use the methods in which expression of SEQ ID NO: 1 or genes which are at least 75% identical with SEQ ID NO: 1 are an indicator of breast or colorectal cancer. The specification does not teach any analysis of variants of SEQ ID NO: 1 which are 75% identical with SEQ ID NO: 1. These variants may include variants which afford a protective effect to the nucleic acid such that they are indicative of lower risk for cancer. The variants also include splice-variants, SNPs, mutations, deletions, insertions which may have different diagnostic implications on the nucleic acids. Without undue and unpredictable experimentation, the skilled artisan would not be aware of which of the variants would have which effects on the risk of breast or colon cancers.

With respect to Claims 44-47, the specification does not teach how expression of SEQ ID NO: 1 or nucleic acids 75% identical with SEQ ID NO: 1 are predictive of

prognosis. The specification does not teach any levels of expression which provide extremely poor prognosis, as opposed to which levels of expression are deemed to be indicative of good prognosis. There are not thresholds or ranges which delineate any prognosis levels for individuals.

The teachings of the specification do not establish that one could actually detect expression of SEQ ID NO: 1 or genes which are at least 75% identical with SEQ ID NO: 1 as an indicator of colorectal or breast cancer. Rather the teachings of the specification assert that SEQ ID NO: 1 is expressed at higher levels in the colon and breast tissue than in other human tissue types, as discussed above. In the absence of guidance from the specification, one skill in the art may look to the teachings of the prior art for enablement of a claimed invention. However, the closest prior art references, namely Beckmann, does not provide support for the use of SEQ ID NO: 1 expression as an indicator of colorectal or breast cancer. Thus, it is unpredictable as to whether one could successfully use the claimed invention, and given the fact that neither the specification nor the prior art provide evidence of a correlation or association between SEQ ID NO: 1 or variants of 75% identity with SEQ ID NO: 1 expression and colorectal or breast cancer, it is further unpredictable as to whether any quantity of experimentation would allow one to practice the claimed invention. Accordingly, it would require undue experimentation for a skilled artisan to use the claimed invention.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 32-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 32-43 are indefinite over the recitation of "said gene(s)". The claim requires determining the expression of a single gene, however, step (b) is directed to comparing the expression of said gene(s). Therefore, it is unclear what genes are being referred to in step (b). Moreover, the method is a method for diagnosing breast or colorectal cancer by comparing expression levels, however, the final process step in the method is wherein "said comparison is used to diagnose breast or colorectal cancer". It is unclear how the comparison will be used. A final process step such as "where in an increase in expression of SEQ ID NO: 1 is indicative of breast or colorectal cancer" would provide a complete method.

B) Claims 44-47 are indefinite because it is unclear how the expression analysis of the gene would be use to determine the prognosis of the individual. It is unclear whether a "high" level of expression is indicative of poor prognosis or whether a "low" level of expression is indicative of good prognosis. Moreover, the claims do not provide any means of determining the threshold of what is indicative of high and low expression,

nor do the claims provide a comparison to a normal sample. Therefore, it is unclear how one would determine the prognosis of an individual.

Conclusion

9. No claims allowable.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of formal matters can be directed to the patent analyst, Pauline Farrier, whose telephone number is (703) 305-3550.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg

Jeanine Goldberg
July 18, 2002

Lisa B. Arthur

LISA B. ARTHUR
PRIMARY EXAMINER
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